facilitating its interaction with ABCG1 and thus allowing increased unloading of cholesterol from lipid-laden macrophages on arterial walls. In experimental models, oral administration of 4F increased PON1 activity in the pre-β-HDL fraction, a fraction not normally associated with PON1 activity, which might explain the protective effect of this peptide. 4F is less effective than native ApoA-I in activating LCAT, so this specific defect in HDL maturation observed in kidney failure is unlikely to be reversed by either 4F or other ApoA-I mimetic peptides. This agent, however, may serve as a pharmacologic tool to reverse abnormalities in HDL structure that accompany renal failure and may perhaps serve as a tool to repair vascular injury.

DISCLOSURE

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It's not over till the last glomerulus forms

Rosemary Thomas[1] and Frederick J. Kaskel[1]

The Brenner hypothesis postulated that low birth weight and decreased nephron number at birth are linked to chronic kidney disease and systemic hypertension in adulthood. To date, little is known about the effect of extrauterine growth retardation (EUGR) on adult kidney disease. Bacchetta *et al.* present novel data using inulin to show a decrease in renal function for premature children with EUGR. The role of protein nutrition and timing in nephrogenesis is discussed.

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Intrauterine growth retardation, influenced by the decreased supply of nutrients to the human fetus and its environment, with resulting low birth weight, was the basis of the Brenner hypothesis. This hypothesis, which states that low birth weight constitutes a risk factor for diseases in later life such as systemic arterial hypertension and chronic kidney disease, built on the Barker hypothesis, which first established a framework for the intrauterine origin of diseases suffered in adulthood. Since the late 1980s and early 1990s, when these theories were introduced, significant work has been generated to support an inversely related causal link between nephron endowment at birth and essential hypertension in adult humans, supporting the ideas of Barker and Brenner as more than hypotheses.[1]

For babies born before 36 weeks of gestation, neonatal intensive care units are expected to replicate intrauterine development. However, many premature infants do not demonstrate the expected intrauterine growth at the time of discharge; this has resulted in a new term: extrauterine growth retardation (EUGR). Clark *et al.* define EUGR as a growth value ≤10th percentile of intrauterine growth expectation based on estimated postmenstrual age in premature neonates (23–34 weeks' estimated gestational age) at the time of discharge from the hospital.[2] To date, the notion of EUGR as a factor in the development of chronic kidney disease or adult-onset systemic arterial hypertension has not been fully developed. As nephrogenesis is not complete until 36 weeks of gestation, the potential effect of EUGR is particularly relevant in premature babies.[3]

In this regard, Bacchetta *et al.*[4] (this issue) report on the renal function of premature babies (birth weight <1000 g and/or <30 weeks of gestation) in a single-center prospective cohort study. Although the authors address measures of blood pressure, kidney size, and tubular function, as others have done in the past, they demonstrate an association between EUGR and decreased glomerular filtration rate (GFR), but within the range of normal in childhood. They postulated that this moderate decrease in GFR may correspond to moderately reduced nephron number, which although asymptomatic in childhood, may have implications in adulthood. Bacchetta *et al.* also noted an association between decreased protein intake at 7 days of life and EUGR in premature babies. Their study is novel in that GFR was measured with the use of an exogenous marker, inulin, resulting in a more accurate assessment of GFR. When prior studies

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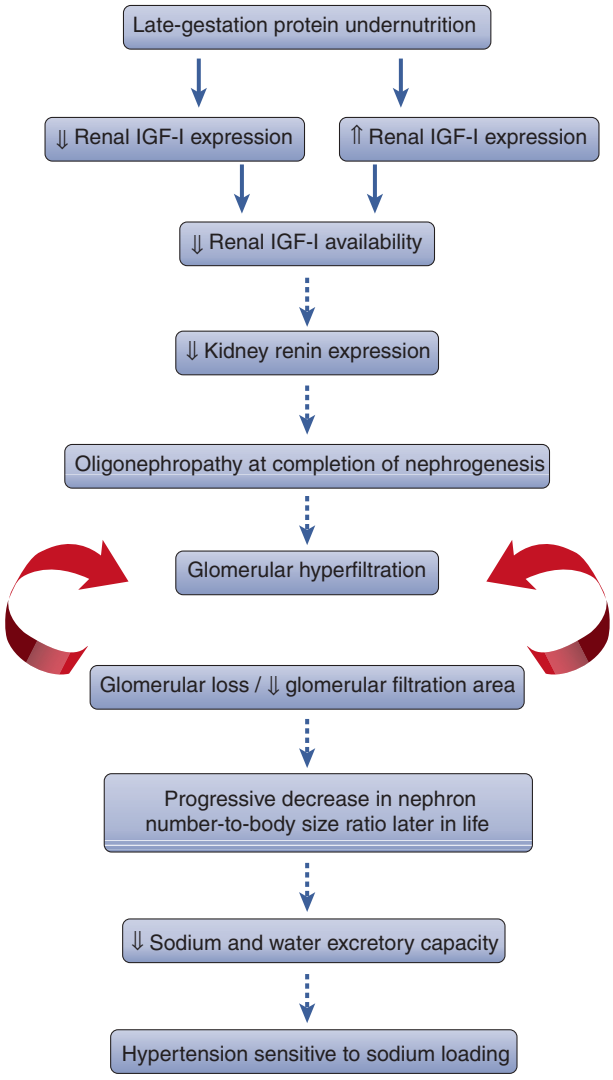

Figure 1 | Depiction of the mechanism of late-gestation protein undernutrition underlying the 'nephron numbers hypothesis' of developmental programming. IGF-1, insulin-like growth factor I; IGFBP-1, insulin-like growth factor-binding protein-I.

investigated renal volume and function in school-age children born preterm or small for gestational age, they estimated renal function by calculating GFR using the Schwartz formula, and found no difference between the two groups.[5] Another problem inherent in prior studies was that they often did not distinguish the preterm babies into groups based on birth weight.

What has been shown clearly is that prenatal factors resulting in intrauterine growth retardation and low birth weight affect long-term renal outcomes. Woods *et al.* have shown with animal models that prenatal maternal nutrition is closely tied to the window of nephrogenesis, which in rats spans a period encompassing the last half of gestation and the first half of lactation.[6] They studied Sprague-Dawley rats that were fed a protein-restricted diet throughout or during the first or second half of pregnancy. They found that glomerular number (per kidney) was decreased in the offspring of rats protein-restricted throughout pregnancy. More specifically, mean arterial pressures were significantly higher in the rats born to mothers protein-restricted throughout or protein-restricted in the second half of pregnancy, rather than in rats protein-restricted early in pregnancy or those fed a normal diet. This evidence points to the importance of timing of adequate protein/calorie provision during the period of nephrogenesis. The reduction in nephron number was also more prominent in male than in female rats.[6]

What has not been shown previously are the effects of EUGR on renal outcomes in humans. Rat models are well suited to studying the effects of EUGR, as the completion of nephrogenesis occurs 10 days after birth.[3] Woods *et al.* showed that intrarenal renin mRNA, renin concentration, and immunostaining for renin were decreased in animals born to mothers restricted in dietary protein. Second, with the goal of establishing a causal relationship, they found that blockade of the angiotensin II type 1 receptor during the first 12 days of postnatal life resulted in a reduced number of glomeruli, reduced renal function, and increased arterial pressure in adult animals. In so doing, Woods *et al.* lent support to the idea that protein restriction during pregnancy in rats causes suppression of the fetal/newborn renin–angiotensin system, which then leads to impaired renal development and a decreased number of nephrons at birth.[7]

A second mechanism by which protein nutrition may impact nephrogenesis has been shown to be mediated by insulin-like growth factor-I (IGF-I) and insulin-like growth factor-binding protein-I (IGFBP-I). IGFBP-I reduces plasma IGF-I bioavailability. Chin *et al.* have reported a positive relationship between dietary protein intake and intrarenal IGF-I expression and renal growth in rats.[8] Comparative data in rats fed isocaloric diets containing variable protein content for 1–7 days showed that rats switched to high-protein diets demonstrated increased IGF-I and decreased IGFBP-I mRNA levels in medullary thick ascending limb lengths, whereas those switched to low-protein diets exhibited the opposite changes in these markers. The increase in renal IGF-I mRNA closely paralleled the significant increases in fractional renal weight, DNA synthesis, and medullary thick ascending limb length, which then mediates growth in the presence of adequate protein substrates. The correlation between changes in renal IGF-I expression and changes in renal growth argues for a role for locally produced IGF-I-mediated protein-induced renal growth.[8] Yeung proposed a unifying hypothesis whereby the depressed IGF-I and intrarenal renin expression and elevated IGFBP-I expression consequent to protein undernutrition lead to reduced nephrogenesis

and oligonephropathy and ultimately contribute to developmental programming for late hypertension (Figure 1).[3]

This work by Bacchetta *et al.*[4] emphasizes the potentially pivotal role of nutrition in the earliest days of extrauterine life. Although neonatal intensive care units are known to be bastions of attention to detail, the study from Japan by Sakurai *et al.* shows that despite the institution of parenteral nutrition and trophic feeding as standard nutritional management strategies for very-low-birth-weight infants, EUGR continues to be a central problem for preterm low-birth-weight infants ≤32 weeks' gestational age. The longer the period of time before complete enteral feeding was achieved, the greater was the risk of EUGR for weight and head circumference.[9] To maximize the potential for nephrogenesis, continued attention needs to be devoted in neonatal intensive care units to maintaining adequate caloric and protein intake in the earliest of postnatal days. This is complicated by conflicting reports that low-nutrient conditions following birth have a positive effect on adult insulin receptivity.[9] Therefore, a dilemma persists between pursuing aggressive and pursuing non-aggressive degrees of nutrition, with the long-term effects of aggressive nutrition requiring further study. What new strategies can be developed to capitalize on the window of opportunity of postnatal nephrogenesis?

The findings of Bacchetta *et al.*[4] are provocative and should stimulate new work in the field, as studies with larger numbers of premature children in a racially diverse ethnic population are needed to validate their findings. The data would be further supported by the determination of GFR by inulin clearance in normal-birth-weight full-term controls. With a larger number of children with EUGR, the likelihood of a difference between males and females can also be assessed to determine whether female gender affords some protection against the detrimental effects of postnatal protein restriction.

DISCLOSURE
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Tissue transglutaminase inhibition as treatment for diabetic glomerular scarring: it's good to be glueless

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Diabetic nephropathy is characterized by enhanced glomerular and tubulointerstitial deposition of extracellular matrix proteins, which are bound together by tissue transglutaminase (TG2). Huang *et al.* demonstrate that infusion of a novel TG2 inhibitor in diabetic rats prevented renal scarring and albuminuria and preserved glomerular filtration rate. These studies confirm the role of TG2 in the pathogenesis of diabetic nephropathy and add to an emerging literature that demonstrates that TG2 is an attractive therapeutic target for sclerosing kidney diseases.

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Diabetes is recognized as the most common cause of chronic kidney disease worldwide, with the majority of incident cases of end-stage renal disease in the United States attributed to diabetic nephropathy. The pathogenesis of diabetic nephropathy is complex but is largely characterized by glomerular fibrosis. The predominant histologic lesion is glomerular enlargement due to deposition of interstitial collagens and a variety of other 'scar matrix' proteins, which accumulate within the thickened glomerular basement membranes in a mesangial pattern and/or as Kimmelstiel-Wilson nodules in the glomerular periphery. Interstitial fibrosis, which is composed of similar extracellular matrix proteins between tubules, is also an important predictor of diabetic nephropathy outcomes. Mainstay therapies such as glucose and blood pressure control can slow diabetic nephropathy progression, and some of these regimens may be particularly effective because the pharmacologic agents

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